3/9/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02757060 Genuine Article#: MA816 Number of References: 28
Title: INHIBITION OF HUMAN LUNG- CANCER CELL-LINE GROWTH BY AN
ANTI-P185(HER2) ANTIBODY
(1)
Author(s): KERN JA; TORNEY L; WEINER D; GAZDAR A; SHEPARD HM; FENDLY B
Corporate Source: UNIV IOWA,DEPT MED,DIV PULM DIS,C-33A GH,200 HAWKINS
DR/IOWA CITY//IA/52242; UNIV PENN,DEPT MED/PHILADELPHIA//PA/19104; UNIV
TEXAS,HLTH SCI CTR,SW MED SCH,DEPT PATHOL/DALLAS//TX/75235; GENENTECH
INC/S SAN FRANCISCO//CA/00000
Journal: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, 1993
, V9, N4 (OCT), P448-454
ISSN: 1044-1549
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CYTOLOGY & HISTOLOGY; BIOCHEMISTRY & MOLECULAR
BIOLOGY; RESPIRATORY SYSTEM
Abstract: p185HER2, the product of the c-erbB-2 or HER2 gene, is a
membrane-bound tyrosine kinase that has structural similarity to the
epidermal growth factor receptor. Functionally, interaction of HER2
with its ligand or p185HER2 antibodies affects the growth and
differentiation of HER2-expressing breast cancer cell lines. As
p185HER2 is also expressed in human lung cancers and human lung
cancer cell lines, we hypothesized that these cell lines would also
respond to p185HER2 antibodies. To test this hypothesis, we cultured
human non-small cell lung cancer cell lines in the presence of a

p185HER2 monoclonal antibody called 4D5. 4D5 inhibited the growth of p185HER2-expressing cell lines in a dose-dependent fashion. In addition, BEAS.2B, a p185HER2-nonexpressing bronchial epithelial cell line, was transfected with the HER2 cDNA, resulting in high-level p185HER2 expression, and growth of BEAS.HER2 was now inhibited by 4D5 exposure. Mechanistically, 4D5 appeared to have a weak agonist effect on the tyrosine kinase function of p185HER2, as exposure of p185HER2-expressing cell lines to 4D5 resulted in increased p185HER2 phosphorylation. Furthermore, inhibition of tyrosine kinase function with Genistein reversed the 4D5-induced growth inhibition. Therefore, 4D5 can regulate the growth of p185HER2-expressing lung cancer cell lines through agonist effects on p185HER2.

Identifiers--KeyWords Plus: TUMOR NECROSIS FACTOR; NEU ONCOGENE; FACTOR-RECEPTOR; MONOCLONAL-ANTIBODY; POINT MUTATION; EXPRESSION; GENE; PROTEIN; C-ERBB-2; PROTOONCOGENE

Research Fronts: 91-1779 005 (C-ERBB-2 PROTEIN EXPRESSION; PARAFFIN-EMBEDDED INVASIVE BREAST-CANCER ; NEU ONCOGENE)

91-0307 001 (NERVE GROWTH-FACTOR RECEPTOR IMMUNOREACTIVITY; HIGH-AFFINITY NGF BINDING REQUIRES COEXPRESSION; CULTURED RAT EMBRYONIC CNS CELLS)

91-0452 001 (INHIBITION OF THE EPIDERMAL GROWTH-FACTOR RECEPTOR TYROSINE KINASE; ALPHA-SUBSTITUTED BENZYLIDENEMALONONITRILE TYRPHOSTINS; EARLY SEA-URCHIN EMBRYOS)

Cited References:

AKIYAMA T, 1987, V262, P5592, J BIOL CHEM
BARGMANN CI, 1986, V45, P649, CELL
BARGMANN CI, 1986, V319, P226, NATURE
COUSSENS L, 1985, V230, P1132, SCIENCE

DIFIORE PP, 1987, V237, P178, SCIENCE
ENRIGHT WJ, 1991, V13, P79, FOCUS
FENDLY BM, 1990, V50, P1550, CANCER RES
HOLMES WE, 1992, V256, P1205, SCIENCE
HUDZIAK RM, 1989, V9, P1165, MOL CELL BIOL
KERN JA, 1992, V6, P359, AM J RESP CELL MOL
KERN JA, 1990, V50, P5184, CANCER RES
NOGUCHI M, 1993, V53, P2035, CANCER
PAAKKO P, 1992, V7, P325, AM J RESP CELL MOL
PELES E, 1992, V69, P205, CELL
REDDEL RR, 1988, V48, P1904, CANCER RES
SARUP JC, 1991, V1, P72, GROWTH REGULAT
SCHECHTER AL, 1984, V312, P513, NATURE
SCHNEIDER PM, 1989, V49, P4968, CANCER RES
SCOTT GK, 1991, V266, P4300, J BIOL CHEM
SEMBA K, 1985, V82, P6497, P NATL ACAD SCI USA
SHEPARD HM, 1991, V11, P117, J CLIN IMMUNOL
SHI D, 1991, V5, P213, MOL CARCINOG
STERN DF, 1988, V8, P3969, MOL CELL BIOL
SUGARMAN BJ, 1985, V230, P943, SCIENCE
TATEISHI M, 1991, V27, P1372, EUR J CANCER
WEINER DB, 1990, V50, P421, CANCER RES
WEINER DB, 1989, V339, P230, NATURE
YAMAMOTO T, 1986, V319, P230, NATURE

3/9/2 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus

04934460 JICST ACCESSION NUMBER: 01A0723890 FILE SEGMENT: JICST-E
Treatment for Progressive Recurrent Breast Cancer by Combination Therapy
of Anti- HER2 Antibody(Herceptin) and Paclitaxel(Taxol).
NAKAJIMA HIROO (1); SAKAGUCHI KOICHI (1); MIZUTA NARUHIKO (1); SAWAI KIYOSHI (1)
(1) Kyotofuidai Naibumpitsunyusengeka
Biotherapy(Tokyo), 2001, VOL.15,NO.3, PAGE.336-339, FIG.1, TBL.1, REF.7
JOURNAL NUMBER: L0028AAT ISSN NO: 0914-2223
UNIVERSAL DECIMAL CLASSIFICATION: 615.277.3.03 615.37.03 616-006-08:615.37
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal

ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication
ABSTRACT: Background: Herceptin is a monoclonal anti-HER2/new cancer gene protein antibody. Previous reports have shown that for progressive recurrent breast cancer with a high level of HER2/neu expression, the curative rate when using Herceptin together with Taxan series agents is higher(over 60%) than treatment with Herceptin only. Based on these reports, we treated 5 progressive recurrent cases with combination therapy of Herceptin and Taxol. Patients and Methods: five recurrent cases were treated(local recurrence: 2 cases; bone metastasis: 4 cases; lungs metastasis: 2; cases brain metastasis: one case; remote lymph node metastasis: one case, including multiple cases). In these cases, HER2/neu expression was more than 2+ by immunohistochemical staining in each dissected tumor have shown that. Among these 5 cases, 3 were previously treated with CAF or CMF. At least 3 cycles of therapy were performed. One cycle included dosages of Herceptin(110mg/body) and Taxol(80mg/m2) every week for 4 weeks followed by an interval for two weeks. Result: In case 1, the skin metastasis disappeared more than 90% with the first cycle, showing a marked effect. However heart toxicity appeared within the second period, and we discontinued this treatment. In the other 4 cases, treatment could be continued without any defined side effects. The curative effect from this therapy at present shows 3 cases with PR(partial response) and NC(no change) in the others. In treating the minimal side effect from Taxol, Syakuyaku-kanzoutou was

effective for the nervous system symptoms typical of this drug.

Discussion: We are currently analyzing the mechanism of the combination

effect in vitro in detail. Upregulation of apoptosis in HER2/neu

positive cancer cells is suggested to be one of the main mechanisms.

(author abst.)

DESCRIPTORS: human(primates); case report; adult(person); woman; breast

tumor ; immunotherapy; drug therapy; combination therapy; antitumor

drug; oncoprotein; monoclonal antibody; antitumor action; recurrence;

neoplasm staging; metastasis; bone tumor ; lung tumor ; brain

tumor ; tumor antigen; repeated administration; tumor regression;

effectiveness; cytotoxicity; neurologic manifestation; side effect;

histological diagnosis; toxicity; Chinese drug; aminoalcohol;

aminocarboxylic acid; olefin compound; carboxylate(ester); hydroxy

ketone; hydroxy acid; polyol; bridged compound; oxygen heterocyclic

compound; alicyclic compound; fatty acid; secondary alcohol; aromatic

carboxylic acid

IDENTIFIERS: cardiotoxicity; Shao-Yao-Gan-Cao-Tang; scirrhous carcinoma

BROADER DESCRIPTORS: reporting; action and behavior; growth stage;

human(sociology); feminity; sex; tumor ; disease; breast disease;

therapy; drug; protein; antibody; pharmacological action; action and

effect; metabasis; tumor process; process; bone disease; bone and

joint disease; respiratory tract tumor ; respiratory tract disease;

lung disease; nervous system neoplasm; nervous system disease; brain

disease; central nervous system disease; antigen; medication method;

administration(biology); property; symptom; clinical laboratory test;
medical examination; inspection; diagnosis; crude drug; amine; alcohol;
hydroxy compound; carboxylic acid; ester; ketone; carbonyl compound;
heterocyclic compound; aliphatic carboxylic acid; aromatic compound
CLASSIFICATION CODE(S): GW16020L; GW22020O; GE03035B

9/3/8 (Item 2 from file: 6)
DIALOG(R)File 6:NTIS

0135106 NTIS Accession Number: PB-175 577/XAB
Preparation of Antigens and Antisera for Influenza Virus Types
(Semiannual progress rept. 1 Sep 66-1 Mar 67)
Beardmore, W. B.
Parke, Davis and Co., Detroit, Mich.
Corp. Source Codes: 276400
1 Mar 67 21p
Journal Announcement: USGRDR6718
This report consistes of pages 2-22. Order as PB-175 576.
Order this product from NTIS by: phone at 1-800-553-NTIS (U.S. customers); (703)605-6000 (other countries); fax at (703)321-8547; and email at orders@ntis.fedworld.gov. NTIS is located at 5285 Port Royal Road, Springfield, VA, 22161, USA.
NTIS Prices: PC A02/MF A01

9/3/19 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09136772 97071273 PMID: 8914198
Formulation development of an antifibrin monoclonal antibody **radiopharmaceutical.**
Kamat MS; Tolman GL; Brown JM
Centocor Inc., Malvern, Pennsylvania 19355, USA.
Pharmaceutical biotechnology (UNITED STATES) **1996** , 9 p343-64, ISSN 1078-0467 Journal Code: BYR
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Complete **17/3/1 (Item 1 from file: 5)**
DIALOG(R)File 5:Biosis Previews(R)

13232322 BIOSIS NO.: 200100439471
Protein formulation.
AUTHOR: Andya James(a); Cleland Jeffrey L; Hsu Chung C; Lam Xanthe M; Overcashier David E; Shire Steven J; Yang Janet Yu-Feng; Wu Sylvia Sau-Yan
AUTHOR ADDRESS: (a)Millbrae, CA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1248 (5):pNo Pagination July 31, 2001
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

17/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13157206 BIOSIS NO.: 200100364355
Modulation of antigenicity related to changes in antibody **flexibility upon** lyophilization.
AUTHOR: Taschner Nicole; Muller Shirley A; Alumella Venkateshwar R; Goldie Kenneth N; Drake Alex F; Aebi Ueli; Arvinte Tudor(a)
AUTHOR ADDRESS: (a)Biotechnology Development and Production, Novartis Pharma AG, CH-4002, Basel: tudor.arvinte@pharma.novartis.com**Switzerland
JOURNAL: Journal of Molecular Biology 310 (1):p169-179 29 June, 2001
MEDIUM: print
ISSN: 0022-2836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

17/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

10793300 BIOSIS NO.: 199799414445
Stability assessment of lyophilized **intravenous immunoglobulin after** reconstitution **in glass containers and poly(vinyl chloride) bags.**
AUTHOR: Parti Rajesh(a); Mankarious Samia
AUTHOR ADDRESS: (a)Stability Assurance, Baxter Healthcare Corp., Hyland Div., 1710 Flower Ave., Duarte, CA 91010**USA
JOURNAL: Biotechnology and Applied Biochemistry 25 (1):p13-18 1997
ISSN: 0885-4513
RECORD TYPE: Abstract
LANGUAGE: English

17/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10354462 BIOSIS NO.: 199698809380
Development of stable lyophilized **monoclonal** antibody **formulations: Effect of excipients on stability.**
AUTHOR: Bam Narendra; Dal Monte Paul R; Duddu Sarma P
AUTHOR ADDRESS: Pharm. Dev., SmithKline Beecham Pharm., King of Prussia, PA 19406**USA
JOURNAL: Abstracts of Papers American Chemical Society 211 (1-2):pBIOT 143 1996
CONFERENCE/MEETING: 211th American Chemical Society National Meeting New Orleans, Louisiana, USA March 24-28, 1996
ISSN: 0065-7727
RECORD TYPE: Citation
LANGUAGE: English

17/3/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10143673 BIOSIS NO.: 199698598591
Degradation of lyophilized **and** reconstituted **MACROSCINT (DTPA-IgG): Precipitation vs glucosylation.**
AUTHOR: Hekman Carla(a); Park Sungae; Teng Wen-Yu; Guzman Norberto A; Rossi Thomas
AUTHOR ADDRESS: (a)Analytical Res. Dev., R. W. Johnson Pharmaceutical Res. Inst., 1000 Route 202, Raritan, NJ 08869**USA
JOURNAL: Journal of Pharmaceutical and Biomedical Analysis 13 (10):p 1249-1261 1995
ISSN: 0731-7085
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

17/3/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10085376 BIOSIS NO.: 199598540294
Safety and immunogenicity of liquid (LIQU) combination of DTP-PRPT vs. a lyophilized **(LYOPH) PRPT** reconstituted **with DTP.**
AUTHOR: Amir J(a); Dagan R; Ethevenaux C; Fritzell B
AUTHOR ADDRESS: (a)Tel-Aviv Univ., Tel-Aviv**Israel
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 35 (0):p170 1995
CONFERENCE/MEETING: 35th Interscience Conference on Antimicrobial Agents and Chemotherapy San Francisco, California, USA September 17-20, 1995
RECORD TYPE: Citation
LANGUAGE: English

17/3/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

08070649 BIOSIS NO.: 000093092097
THE INFLUENCE OF SUCROSE DEXTRAN AND HYDROXYPROPYL-BETA-CYCLODEXTRIN AS LYOPROTECTANTS FOR A FREEZE-DRIED MOUSE IGG-2A MONOCLONAL ANTIBODY **MN12**
AUTHOR: RESSING M E; JISKOOT W; TALSMA H; VAN INGEN C W; BEUVERY E C; CROMMELIN D J A
AUTHOR ADDRESS: DEP. PHARMACEUTICS, FAC. PHARM., UNIV. UTRECHT, BOX 80082, 3508 TB UTRECHT, NETH.
JOURNAL: PHARM RES (N Y) 9 (2). 1992. 266-270. 1992
FULL JOURNAL NAME: Pharmaceutical Research (New York)
CODEN: PHREE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH **17/3/33 (Item 33 from file: 5)**
DIALOG(R)File 5:Biosis Previews(R)

03277024 BIOSIS NO.: 000072005127
LYOPHILIZED **HYPER IMMUNE EQUINE SERUM AS A SOURCE OF** ANTIBODIES **FOR NEO NATAL FOALS**
AUTHOR: BURTON C; HINTZ H F; KEMEN M J; HOLMES D F
AUTHOR ADDRESS: DEP. CLIN. SCI., COLL. VET. MED., CORNELL UNIV., ITHACA, NY 14853.
JOURNAL: AM J VET RES 42 (2). 1981. 308-310. 1981
FULL JOURNAL NAME: American Journal of Veterinary Research
CODEN: AJVRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH
17/3/41 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09465010 Genuine Article#: 408VL No. References: 34
Title: A specific molar ratio of stabilizer to protein is required for storage stability of a lyophilized **monoclonal** antibody
Author(s): Cleland JL (REPRINT) ; Lam X; Kendrick B; Yang J; Yang TH; Overcashier D; Brooks D; Hsu C; Carpenter JF
Corporate Source: Genentech Inc,Pharmaceut R&D,1 DNA Way/S San Francisco//CA/94070 (REPRINT); Genentech Inc,Pharmaceut R&D,S San Francisco//CA/94070; Amgen Inc,Dept Pharmaceut,Thousand Oaks//CA/91320; Genentech Inc,Qual Control,S San Francisco//CA/94070; Univ Colorado,Hlth Sci Ctr, Dept Pharmaceut Sci,Denver//CO/
Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 2001, V90, N3 (MAR), P310-321
ISSN: 0022-3549 Publication date: 20010300
Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)
17/3/53 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01199018 Genuine Article#: GD532 No. References: 10
Title: STABLE LYOPHILIZED **REAGENTS FOR THE SERUM FERRITIN ASSAY**
Author(s): WORWOOD M; THORPE SJ; HEATH A; FLOWERS CH; COOK JD
Corporate Source: UNIV WALES COLL MED,DEPT HAEMATOL/CARDIFF CF4 4XN/S GLAM/WALES/; NATL INST BIOL STAND & CONTROLS/S MIMMS EN6 3QG/HERTS/ENGLAND/; UNIV KANSAS,MED CTR,DEPT INTERNAL MED,HAEMATOL SECT/KANSAS CITY//KS/66103
Journal: CLINICAL AND LABORATORY HAEMATOLOGY, 1991, V13, N3, P297-305
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

17/3/73 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

12895576 PASCAL No.: 97-0160846
Stability assessment of lyophilized **intravenous immunoglobulin after** reconstitution **in glass containers and poly(vinyl chloride) bags. Commentary**
SAPAN C V comment; PARTI R; MANKARIOUS S

NABI (R) , P.O. Box 310701, Boca Raton, FL 33431-0701, United States; Stability Assurance, Baxter Healthcare Corporation, Hyland Division, 1710 Flower Avenue, Duarte, CA 91010, United States; Biopharmaceutics, Baxter Healthcare Corporation, Hyland Division, 1710 Flower Avenue, Duarte, CA 91010, United States
Journal: Biotechnology and applied biochemistry, 1997, 25 (1) 9-11,13-18 (9 p.)
Language: English

17/3/75 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09318319 97218594 PMID: 9066031
Immunogenicity and safety of a liquid combination of DTP-PRP-T [corrected] vs lyophilized **PRP-T** reconstituted **with DTP.**
Amir J; Melamed R; Bader J; Ethevenaux C; Fritzell B; Cartier JR; Arminjon F; Dagan R
Department of Pediatrics C, Schneider Children's Medical Center of Israel, Petah Tiqva, Israel.
Vaccine (ENGLAND) Feb 1997, 15 (2) p149-54, ISSN 0264-410X Journal Code: X60
Erratum in Vaccine 1997 Nov;15(16) 1813
Languages: ENGLISH
Document type: Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial
Record type: Completed

17/3/78 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04728023 81253873 PMID: 6266291
Lyophilized **hyperimmune equine serum as a source of** antibodies **for neonatal foals.**
Burton SC; Hintz HF; Kemen MJ; Holmes DF
American journal of veterinary research (UNITED STATES) Feb 1981, 42 (2) p308-10, ISSN 0002-9645 Journal Code: 40C
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

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          27433  LYOPHILIZ?
         333309  BULK?
        3763387  AGENT?
           1389  BULK?(W)AGENT?
         493249  CARRIER
         128806  CARRY
        2499525  ANTIBOD?
      S1      60  LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND
                  ANTIBOD?
?s her2(s)antibod?
           4806  HER2
        2499525  ANTIBOD?
      S2    1440  HER2(S)ANTIBOD?
?s treat?(w)(cancer? or neoplas? or malignat?)
Processing
Processed  10 of  12 files ...
Completed processing all files
        8793864  TREAT?
        2524718  CANCER?
        1980117  NEOPLAS?
            168  MALIGNAT?
      S3    8848  TREAT?(W)(CANCER? OR NEOPLAS? OR MALIGNAT?)
?s s1 and s2 and s3
             60  S1
           1440  S2
           8848  S3
      S4       0  S1 AND S2 AND S3
?s s1 and s2
             60  S1
           1440  S2
      S5       5  S1 AND S2
?t /full/all
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5/9/1 (Item 1 from file: 5)

12107717 BIOSIS NO.: 199900402566

Lyophilization **of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse.**

AUTHOR: Overcashier David E(a); Patapoff Thomas W; Hsu Chung C
AUTHOR ADDRESS: (a)Department of Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Fra**USA

JOURNAL: Journal of Pharmaceutical Sciences 88 (7):p688-695 July, 1999
ISSN: 0022-3549
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: During the **lyophilization** process, formulations containing protein, **bulking agent** , or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMAb **HER2** , trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature

affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 mum) holes in their platelike structures after **lyophilization** . The quantity of holes was higher for material dried at higher temperature. The collapse temperature (Tc) of a material appeared to play a role in the process, as lower Tc was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

REGISTRY NUMBERS: 57-50-1: SUCROSE; 99-20-7: TREHALOSE
DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Methods and Techniques; Pharmacology
CHEMICALS & BIOCHEMICALS: protein--pharmaceutical formulations; recombinant humanized **antibody HER2** ; sucrose; trehalose
METHODS & EQUIPMENT: fluorescence microscopy--analytical method; freeze-drying microscopy--analytical method; **lyophilization** -- biochemical method; scanning electron microscopy--analytical method
MISCELLANEOUS TERMS: water vapor flow
CONCEPT CODES:
22002 Pharmacology-General
10050 Biochemical Methods-General
10060 Biochemical Studies-General
23001 Temperature: Its Measurement, Effects and Regulation-General Measurement and Methods
10502 Biophysics-General Biophysical Studies

5/9/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07841406 Genuine Article#: 214HP Number of References: 20
Title: Lyophilization **of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse**
Author(s): Overcashier DE (REPRINT) ; Patapoff TW; Hsu CC
Corporate Source: GENENTECH INC,DEPT PHARMACEUT RES & DEV, 1 DNA WAY/S SAN FRANCISCO//CA/94080 (REPRINT)
Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 1999, V88, N7 (JUL), P688-695
ISSN: 0022-3549 Publication date: 19990700
Publisher: AMER PHARMACEUTICAL ASSN, 2215 CONSTITUTION AVE NW, WASHINGTON, DC 20037
Language: English Document Type: ARTICLE
Geographic Location: USA
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CHEMISTRY, MEDICINAL; PHARMACOLOGY & PHARMACY; CHEMISTRY
Abstract: During the **lyophilization** process, formulations containing protein, **bulking agent** , or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMAb **HER2** , trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy

techniques, to possess small (2-20 mu m) holes in their platelike structures after **lyophilization** . The quantity of holes was higher for material dried at higher temperature. The collapse temperature (T-c) of a material appeared to play a role in the process, as lower T-c was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

Identifiers--KeyWord Plus(R): TEMPERATURE; MOISTURE; STAGE

Cited References:

CARPENTER JF, 1989, V28, P3916, BIOCHEMISTRY-US
CHANG BS, 1995, V12, P831, PHARMACEUT RES
CROWE LM, 1996, V71, P2087, BIOPHYS J
FENDLY BM, 1990, V50, P1550, CANCER RES
FLETCHER NH, 1970, P143, CHEM PHYSICS ICE
HSU CC, 1996, V85, P70, J PHARM SCI
JANSCO G, 1970, V74, P2984, J PHYS CHEM-US
LIVESEY RG, 1987, V41, P169, J PARENTER SCI TECHN
MACKENZIE AP, 1975, P277, FREEZE DRYING ADV FO
MILTON N, 1997, V51, P7, PDA J PHARM SCI TECH
NAIL SL, 1980, V34, P358, J PARENTER DRUG ASS
PIKAL MJ, 1991, V74, P21, DEV BIOL STAND
PIKAL MJ, 1990, V62, P165, INT J PHARM
PIKAL MJ, 1985, V39, P115, J PARENTER SCI TECHN
PIKAL MJ, 1983, V72, P635, J PHARM SCI
PIKAL MJ, 1984, V73, P1224, J PHARM SCI
PIKAL MJ, 1997, V51, P17, PDA J PHARM SCI TECH
PRESTRELSKI SJ, 1995, V12, P1250, PHARMACEUT RES
ROY ML, 1989, V43, P60, J PARENT SCI TECHN
TOWNSEND MW, 1988, V42, P190, J PARENTER SCI TECHN

5/9/3 (Item 1 from file: 73)

07761547 EMBASE No: 1999244329

Lyophilization **of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse**

Overcashier D.E.; Patapoff T.W.; Hsu C.C.
D.E. Overcashier, Dept. of Pharmaceut. Res. and Devt., Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 United States
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Journal of Pharmaceutical Sciences (J. PHARM. SCI.) (United States) 1999, 88/7 (688-695)
CODEN: JPMSA ISSN: 0022-3549
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 20

During the **lyophilization** process, formulations containing protein, **bulking agent** , or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMAb **HER2** , trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose

and sucrose were seen, by both microscopy techniques, to possess small (2-20 mum) holes in their platelike structures after **lyophilization** . The quantity of holes was higher for material dried at higher temperature. The collapse temperature (T(c)) of a material appeared to play a role in the process, as lower T(c) was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

MEDICAL DESCRIPTORS:
*freeze drying; *drug formulation
water vapor; scanning electron microscopy; fluorescence microscopy; temperature; article
SECTION HEADINGS:
039 Pharmacy

5/9/4 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

14180821 PASCAL No.: 99-0379550
Lyophilization **of protein formulations in vials : Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse**
OVERCASHIER D E; PATAPOFF T W; HSU C C
Department of Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States
Journal: Journal of pharmaceutical sciences, 1999, 88 (7) 688-695
ISSN: 0022-3549 CODEN: JPMSAE Availability: INIST-3209A; 354000085827110050
No. of Refs.: 20 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
square During the **lyophilization** process, formulations containing protein, **bulking agent** , or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMAb **HER2** , trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 mu m) holes in their platelike structures after **lyophilization** . The quantity of holes was higher for material dried at higher temperature. The collapse temperature (T SUB c) of a material appeared to play a role in the process, as lower T SUB c was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

English Descriptors: Freeze drying; Dosage form; Pharmaceutical technology; **Antibody** ; Recombinant protein; Trehalose; Histidine; Polysorbate; Human ; Resistance; Mass transfer; Sublimation

French Descriptors: Lyophilisation; Forme pharmaceutique; Technologie pharmaceutique; Anticorps; Proteine recombinante; Trehalose; Histidine;

Polysorbate; Homme; Resistance; Transfert masse; Sublimation

Classification Codes: 002B02A03

5/9/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10196849 99322067 PMID: 10393566

Lyophilization **of protein formulations in vials: investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse.**

Overcashier DE; Patapoff TW; Hsu CC
Department of Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.

Journal of pharmaceutical sciences (UNITED STATES) Jul 1999, 88 (7) p688-95, ISSN 0022-3549 Journal Code: JO7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Subfile: INDEX MEDICUS

During the **lyophilization** process, formulations containing protein, **bulking agent** , or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMAb **HER2** , trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 microm) holes in their platelike structures after **lyophilization** . The quantity of holes was higher for material dried at higher temperature. The collapse temperature (Tc) of a material appeared to play a role in the process, as lower Tc was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

Tags: Support, Non-U.S. Gov't
Descriptors: *Freeze Drying; *Proteins--chemistry--CH; Microscopy; Temperature; Volatilization
CAS Registry No.: 0 (Proteins)
Record Date Created: 19990729

?ds

Set	Items	Description
S1	60	LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND ANTIBOD?
S2	1440	HER2(S)ANTIBOD?
S3	8848	TREAT?(W)(CANCER? OR NEOPLAS? OR MALIGNAT?)
S4	0	S1 AND S2 AND S3
S5	5	S1 AND S2

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Set     Items   Description
S1         60   LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND AN-
               TIBOD?
S2       1440   HER2(S)ANTIBOD?
S3       8848   TREAT?(W)(CANCER? OR NEOPLAS? OR MALIGNAT?)
S4          0   S1 AND S2 AND S3
S5          5   S1 AND S2
S6          0   S1 AND S3
S7         47   RD S1 (unique items)
S8   64506112   PY<=1996
S9         33   S8 AND S7
S10      2251   LYOPHILIZ? AND ANTIBOD?
S11      1345   RD (unique items)
S12      1118   S11 AND S8
S13   2235029   (BULK?(W)AGENT OR CARRIER? OR CARR?)
S14    164393   RECONSTITUT?
S15   6119450   D
S16   6119450   D
S17        90   S14 AND S11
?s s2 and s3
            1440  S2
            8848  S3
     S18       7  S2 AND S3
?rd
...completed examining records
     S19       4  RD (unique items)
?t /full/all
 19/9/1     (Item 1 from file: 34)
DIALOG(R)File  34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

09978608   Genuine Article#: 472RZ   Number of References: 71
Title: Mechanism of action of anti- HER2 monoclonal antibodies
Author(s): Baselga J (REPRINT) ; Albanell J
Corporate Source: Hosp Gen Univ Vall Hebron,Dept Med Oncol, Med Oncol
    Serv,Psg Vall Hebron 119-129/Barcelona 08035//Spain/ (REPRINT); Hosp
    Gen Univ Vall Hebron,Dept Med Oncol, Med Oncol Serv,Barcelona
    08035//Spain/
Journal: ANNALS OF ONCOLOGY, 2001, V12, 1, P35-41
ISSN: 0923-7534   Publication date: 20010000
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA
    DORDRECHT, NETHERLANDS
Language: English   Document Type: ARTICLE
Geographic Location: Spain
Journal Subject Category: ONCOLOGY
Abstract: The search for new methods of treating  cancer , combined with
    advances in our understanding of carcinogenesis, molecular biology and
    technology, has resulted in the development of novel biologic agents
    with proven clinical efficacy. One such agent is trastuzumab
    (Herceptin), a humanized monoclonal antibody  that targets the human
    epidermal growth factor receptor-2 (HER2 ). HER2  is a member of a
    family of receptors that interact with each other and various ligands
    to stimulate various intracellular signal transduction pathways
    involved in cell growth control. HER2  is overexpressed in 20%-30% of
    women with breast cancer and is associated with aggressive tumor
    characteristics and poor prognosis. Trastuzumab is the first humanized
    monoclonal antibody  to be approved for therapeutic use and the first
    oncogene-targeted treatment with proven survival benefit in women with
   HER2 -positive metastatic breast cancer. However, its mechanism of
    action has not been fully characterized and appears to be complex. This
    paper reviews current knowledge of the mechanism of action of
    trastuzumab, including HER2  protein downregulation, prevention of
   HER2 -containing heterodimer formation, initiation of G1 arrest and
    induction of p27, prevention of HER2  cleavage, inhibition of
    angiogenesis, and induction of immune mechanisms. The significance of
    these mechanisms for selection of concomitant chemotherapy is also
    considered.
Descriptors--Author Keywords: HER2 ;  mechanism of action ; monoclonal
```

antibodies ; signal transduction ; Herceptin ; trastuzumab
Identifiers--KeyWord Plus(R): METASTATIC BREAST-CANCER; EPIDERMAL GROWTH-FACTOR; TUMOR-CELL-LINES; TYROSINE KINASE-ACTIVITY; CARCINOMA CELLS; FACTOR RECEPTOR; EXTRACELLULAR DOMAIN; C-ERBB-2 ONCOPROTEIN; NECROSIS FACTOR; ERBB RECEPTORS
Cited References:

*EARL BREAST CANC, 1998, V352, P930, LANCET
*EARL BREAST CANC, 1988, V319, P1681, NEW ENGL J MED
*EARL BREAST CANC, 1990, V1, WORLDW EV 1985 1990
AKIYAMA T, 1986, V232, P1644, SCIENCE
ALROY I, 1997, V410, P83, FEBS LETT
BASELGA J, 1998, V58, P2825, CANCER RES
BAULIDA J, 1996, V271, P5251, J BIOL CHEM
BENZ CC, 1992, V24, P85, BREAST CANCER RES TR
BRODOWICZ T, 1997, V73, P875, INT J CANCER
CARRAWAY KL, 1997, V387, P512, NATURE
CARTER P, 1992, V89, P4285, P NATL ACAD SCI USA
CHAZIN VR, 1992, V7, P1859, ONCOGENE
CHRISTIANSON TA, 1998, V58, P5123, CANCER RES
COBLEIGH MA, 1999, V17, P2639, J CLIN ONCOL
CODONYSERVAT J, 1999, V59, P1196, CANCER RES
CODONY J, 1999, V40, P369, P AM ASS CANC RES AN
COUSSENS L, 1985, V230, P1132, SCIENCE
DESANTES K, 1992, V52, P1916, CANCER RES
DREBIN JA, 1985, V41, P695, CELL
FAN Z, 1998, V10, P67, CURR OPIN ONCOL
FENDLY BM, 1990, V50, P1550, CANCER RES
FISHER B, 1994, V18, P63, WORLD J SURG
FORNIER M, 1999, V13, P647, ONCOLOGY-NY
GOLDENBERG MM, 1999, V21, P309, CLIN THER
GRAUSPORTA D, 1997, V16, P1647, EMBO J
GREENBERG PAC, 1996, V14, P2197, J CLIN ONCOL
HANCOCK MC, 1991, V51, P4575, CANCER RES
HARRIS LN, 1996, V15, P108, P ASCO
HOLASH J, 1999, V18, P5356, ONCOGENE
HORTOBAGYI GN, 1999, V26, P11, SEMIN ONCOL S12
HOTALING TE, 1996, V37, P471, P ANN M AM ASS CANC
HUANG HJS, 1997, V272, P2927, J BIOL CHEM
HUDZIAK RM, 1988, V85, P5102, P NATL ACAD SCI USA
HUDZIAK RM, 1989, V9, P1165, MOL CELL BIOL
JURIANZ K, 1999, V42, P209, IMMUNOPHARMACOLOGY
KASPRZYK PG, 1992, V52, P2771, CANCER RES
KLAPPER LN, 1997, V14, P2099, ONCOGENE
KRAUS MH, 1987, V6, P605, EMBO J
KUMAR R, 1991, V11, P979, MOL CELL BIOL
LANE HA, 2001, V12, PS21, ANN ONCOL S1
LEITZEL K, 1995, V13, P1129, J CLIN ONCOL
LEWIS GD, 1993, V37, P255, CANCER IMMUNOL IMMUN
LIN YZJ, 1991, V6, P639, ONCOGENE
MILSTEIN C, 1975, V256, P495, NATURE
NAGY P, 1999, V5, P255, PATHOL ONCOL RES
NICULESCU F, 1992, V140, P1039, AM J PATHOL
NORTON L, 1999, V18, P483, P AM SOC CLIN ONCOL
OLAYIOYE MA, 1998, V18, P5042, MOL CELL BIOL
PEGRAM M, 1999, V18, P2241, ONCOGENE
PEGRAM MD, 1997, V38, P602, P AM ASSOC CANC RES
PEREZ EA, 1999, V26, P1, SEMIN ONCOL S12
PETIT AMV, 1997, V151, P1523, AM J PATHOL
PIETRAS RJ, 1994, V9, P1829, ONCOGENE
PINKASKRAMARSKI R, 1997, V15, P2803, ONCOGENE
POPESCU NC, 1989, V4, P362, GENOMICS
PUPA SM, 1993, V8, P2917, ONCOGENE
RAK JW, 1995, V6, P3, ANTI-CANCER DRUG
REESE D, 1996, V37, P AM ASS CANC RES
SARUP JC, 1991, V1, P72, GROWTH REGULAT
SEGATTO O, 1988, V8, P5570, MOL CELL BIOL
SLAMON DJ, 1989, V244, P707, SCIENCE
SLAMON D, 1998, V17, P98, P AM SOC CLIN ONCOL

SLAMON DJ, 1987, V235, P177, SCIENCE
SLIWKOWSKI MX, 1994, V269, P14661, J BIOL CHEM
SLIWKOWSKI MX, 1999, V26, P60, SEMIN ONCOL S12
STANCOVSKI I, 1991, V88, P8691, P NATL ACAD SCI USA
TOKUDA Y, 1996, V72, P1362, BRIT J CANCER
UENO NT, 1997, V15, P953, ONCOGENE
VENTER DJ, 1987, V2, P69, LANCET
YAMAKAWA M, 1994, V73, P2808, CANCER
YU DH, 1998, V2, P581, MOL CELL

19/9/2 (Item 1 from file: 76)

02396129 4563089

Antibody-induced apoptosis

Arakawa, T.; Kita, Y.
Amgen Inc.
PATENT NUMBER: US 5783186
(1998)
DOCUMENT TYPE: Patent LANGUAGE: ENGLISH
SUBFILE: Medical and Pharmaceutical Biotechnology Abstracts

Anti-**Her2** **antibodies** which induce apoptosis in **Her2** expressing cells are disclosed. The **antibodies** are used to "tag" **Her2** overexpressing tumors for elimination by the host immune system. Also disclosed are hybridoma cell lines producing the **antibodies** , methods for **treating** **cancer** using the **antibodies** , and pharmaceutical compositions.

DESCRIPTORS: Patents; Apoptosis; Monoclonal antibodies; Hybridoma; Tumors; HER2 protein
SECTION HEADING: 33050 -- Patents; 33375 -- Antibodies

19/9/3 (Item 1 from file: 399)

135288636 CA: 135(20)288636p PATENT

Synergistic methods and compositions for treating cancer using two or more anticancer agents

INVENTOR(AUTHOR): Lee, Francis Y.
LOCATION: USA
ASSIGNEE: Bristol-Myers Squibb Company
PATENT: PCT International ; WO 200172721 A2 DATE: 20011004
APPLICATION: WO 2001US9193 (20010322) *US PV192278 (20000327)
PAGES: 81 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07D-243/00A
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG ; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA226006 Biomolecules and Their Synthetic Analogs
CA201XXX Pharmacology
CA228XXX Heterocyclic Compounds (More Than One Hetero Atom)
CA230XXX Terpenes and Terpenoids
CA263XXX Pharmaceuticals
IDENTIFIERS: imidazolylbenzodiazepine anticancer synergistic treatment cancer, chemotherapy synergism epothilone baccatin imidazolylbenzodiazepine
DESCRIPTORS:
Antibodies...
anti-Her2 and imclone antibody C225; synergistic methods using two or more anticancer agents for treating cancer

Enzymes,biological studies...
antineoplastic; synergistic methods using two or more anticancer agents for treating cancer
Intestine,neoplasm...
colon, carcinoma, inhibitors; synergistic methods using two or more anticancer agents for treating cancer
Antitumor agents...
colon carcinoma; synergistic methods using two or more anticancer agents for treating cancer
Intestine,neoplasm...
colon, inhibitors; synergistic methods using two or more anticancer agents to kill a colon cancer xenograft
Antitumor agents...
colon; synergistic methods using two or more anticancer agents to kill a colon cancer xenograft
Chemotherapy...
combination; synergistic methods using two or more anticancer agents for treating cancer
Nucleosides,biological studies...
cytotoxic; synergistic methods using two or more anticancer agents for treating cancer
Anthracyclines...
drug; synergistic methods using two or more anticancer agents for treating cancer
Platelet-derived growth factors...
inhibitors; synergistic methods using two or more anticancer agents for treating cancer
Drug delivery systems...
injections; synergistic methods using two or more anticancer agents for treating cancer
Antitumor agents...
mammary gland; synergistic methods using two or more anticancer agents for treating cancer
Stabilizing agents...
microtubule; synergistic methods using two or more anticancer agents for treating cancer
Mammary gland... Prostate gland...
neoplasm, inhibitors; synergistic methods using two or more anticancer agents for treating cancer
Coordination compounds...
platinum; synergistic methods using two or more anticancer agents for treating cancer
Antitumor agents...
prostate gland; synergistic methods using two or more anticancer agents for treating cancer
Antitumor agents...
squamous cell carcinoma; synergistic methods using two or more anticancer agents for treating cancer
Cooperative phenomena...
synergism; synergistic methods using two or more anticancer agents for treating cancer
Alkylating agents,biological... Antitumor agents...
Hormones,animal,biological studies... Interferons... Interleukins...
Radiotherapy... Taxanes...
synergistic methods using two or more anticancer agents for treating cancer
Steroids,biological studies...
synthetic analog; synergistic methods using two or more anticancer agents for treating cancer
Alkaloids,biological studies...
vinca, drug; synergistic methods using two or more anticancer agents for treating cancer

CAS REGISTRY NUMBERS:

66-22-8 biological studies, synergistic methods using two or more anticancer agents for treating cancer
12794-10-4DP derivs., synergistic methods using imidazolylbenzodiazepine and two or more anticancer agents for treating cancer
91-18-9 drug; synergistic methods using two or more anticancer agents for

treating cancer
9039-48-9 80449-02-1 127464-60-2 137632-03-2 141907-41-7 142243-02-5
142805-58-1 340830-03-7 inhibitors; synergistic methods using two or more anticancer agents for treating cancer
50-07-7 50-18-0 50-24-8 50-44-2 51-21-8 52-24-4 53-03-2 54-62-6
56-53-1 57-22-7 57-63-6 58-05-9 58-18-4 58-22-0 59-05-2 68-96-2
71-58-9 76-43-7 79-22-1 83-43-2 104-94-9 108-24-7 124-94-7
125-84-8 147-94-4 148-82-3 518-28-5 521-12-0 528-74-5 569-57-3
595-33-5 630-19-3 645-05-6 671-16-9 801-52-5 865-21-4 968-93-4
994-30-9 1066-35-9 2410-93-7 2998-57-4 3778-73-2 4342-03-4
4375-07-9 7689-03-4 7751-38-4 9015-68-3 10540-29-1 11056-06-7
13311-84-7 15228-71-4 15663-27-1 17902-23-7 19810-31-2 20830-81-3
23214-92-8 23360-92-1 24424-99-5 29767-20-2 32981-86-5 33069-62-4
33419-42-0 41575-94-4 50935-04-1 52128-35-5 53643-48-4 53714-56-0
65271-80-9 65807-02-5 82855-09-2 89778-26-7 90357-06-5 95058-81-4
100286-90-6 114977-28-5 117091-64-2 123948-87-8 127943-53-7
152044-53-6 152044-54-7 153436-54-5 160237-25-2 172481-83-3
180288-69-1 183321-74-6 184475-35-2 186692-73-9 189453-10-9
195981-08-9 195982-55-9 195982-72-0 195987-41-8 195987-42-9
208518-52-9P 219989-84-1 219990-27-9P 252916-29-3 257933-82-7
280578-48-5P 280578-49-6P 286380-52-7 324743-03-5P 324743-04-6P
324743-05-7P 324743-06-8P 324743-07-9P 324743-08-0P 324743-09-1P
335664-79-4 345627-80-7 345627-82-9 355113-84-7P 355113-86-9P
355113-87-0P 355113-88-1P 355113-98-3P 364357-69-7 364357-70-0
364357-72-2 364357-73-3 364357-75-5P 364357-77-7P 364357-78-8P
364357-79-9 364357-80-2 364357-82-4 364357-83-5 synergistic methods using two or more anticancer agents for treating cancer

19/9/4 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130336963 CA: 130(25)336963p PATENT
Methods and compositions comprising glycoprotein glycoforms
INVENTOR(AUTHOR): Raju, T. Shantha
LOCATION: USA
ASSIGNEE: Genentech, Inc.
PATENT: PCT International ; WO 9922764 A1 DATE: 19990514
APPLICATION: WO 98US21925 (19981016) *US 962497 (19971031)
PAGES: 52 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; C07K-016/00B; C12P-021/00B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA215003 Immunochemistry
IDENTIFIERS: glycoprotein antibody IgG immunoadhesin cancer therapy
DESCRIPTORS:
Tumor necrosis factors...
chimeric; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.
Fusion proteins(chimeric proteins)...
glyco-; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.
Immunoglobulins...
immunoadhesins; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.
Antibodies... Antitumor agents... Buffers... CD20(antigen)... Containers... Glycoproteins(general),biological studies... IgE... IgG1... IgG... Labels ... Monoclonal antibodies... neu(receptor)... Salts,biological studies...

prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

CAS REGISTRY NUMBERS:

59-23-4 biological studies, activated; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

7439-96-5 7440-39-3 7440-70-2 biological studies, prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

2956-16-3 9031-68-9 9054-94-8 127464-60-2 prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

20/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10096040 BIOSIS NO.: 199598550958
Phase I trial of 2B1, a bispecific monoclonal antibody targeting c-erbB-2 and Fc-gamma-RIII.
AUTHOR: Weiner Louis M(a); Clark Joseph I; Davey Monica; Li Wei S; De Palazzo Irma Garcia; Ring David B; Alpaugh R Katherine
AUTHOR ADDRESS: (a)Dep. Med. Oncol., Fox Chase Cancer Cent., 7701 Burholme Ave, Philadelphia, PA 19111**USA
JOURNAL: Cancer Research 55 (20):p4586-4593 **1995**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

20/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09069650 BIOSIS NO.: 199497078020
Monoclonal antibodies directed to the erbB-2 receptor inhibit in vivo tumour cell growth.
AUTHOR: Harwerth I-M; Wels W; Schlegel J; Mueller M; Hynes N E(a)
AUTHOR ADDRESS: (a)Friedrich Miescher Inst., PO Box 2543, CH-4002 Basel** Switzerland
JOURNAL: British Journal of Cancer 68 (6):p1140-1145 **1993**
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

20/3/17 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01381999 Genuine Article#: GU439 No. References: 49
Title: CHARACTERIZATION OF AN ANTI-P185HER2 MONOCLONAL-ANTIBODY THAT STIMULATES RECEPTOR FUNCTION AND INHIBITS TUMOR-CELL GROWTH
Author(s): SARUP JC; JOHNSON RM; KING KL; FENDLY BM; LIPARI MT; NAPIER MA; ULLRICH A; SHEPARD HM
Corporate Source: GENENTECH INC,DEPT CELL BIOL,460 POINT SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT CELL BIOL,460 POINT SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT DEV BIOL/S SAN FRANCISCO//CA/94080; MAX PLANCK INST BIOCHEM/D-8033 MARTINSRIED//FEDREP GER/
Journal: GROWTH REGULATION, **1991** , V1, N2, P72-82
Language: ENGLISH Document Type: ARTICLE (Abstract Available) **20/3/18 (Item 1 from**
DIALOG(R)File 71:ELSEVIER BIOBASE

00295954 95109333
Engineering high affinity humanized anti-p185(HER2)/anti-CD3 F(ab')inf 2 for efficient lysis of p185(HER2) overexpressing tumor cells
Zhu Z.; Lewis G.D.; Carter P.
ADDRESS: P. Carter, Genentech Inc, 460 Point San Bruno Boulevard, South San Francisco, CA 94080, United States
Journal: International Journal of Cancer, 62/3 (319-324), **1995** , United States
PUBLICATION DATE: 19950000
CODEN: IJCNA
ISSN: 0020-7136
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

CLASSIFICATION CODE AND DESCRIPTION:
87.4.3.5 - CANCER RESEARCH / **TREATMENT** / Immunotherapy / Passive
86.9.3.5 - IMMUNOLOGY AND INFECTIOUS DISEASES / TUMOUR IMMUNOLOGY / Tumour

Immunotherapy / Passive 20/3/28 **(Item 1 from file: 144)**
DIALOG(R)File 144:Pascal

09834477 PASCAL No.: 92-0036806
Monoclonal antibody **therapy of human cancer : taking the** HER2 **protooncogene to the clinic**
MICHAEL SHEPARD H; LEWIS G D; SARUP J C; FENDLY B M; MANEVAL D; MORDENTI J; FIGARI I; KOTTS C E; PALLADINO M A JR; ULLRICH A; SLAMON D
Genentech. Inc., dep. development biology, South San Francisco CA 94080, USA
Journal: Journal of clinical immunology, **1991** , 11 (3) 117-127
Language: English

```
Processing
         2889337  TISSUE
         4376600  TYPE?
           29828  TISSUE(W)TYPE?
         4053379  ORGAN?
        10741901  CELL?
         4376600  TYPE?
          311814  CELL?(W)TYPE?
      S5 4342875  (TISSUE(W)TYPE? OR ORGAN? OR CELL?(W)TYPE?)
?ds

Set     Items   Description
S1       1425   HER2(S)EXPRESSION
S2        541   RD (unique items)
S3   41149634   PY<1996
S4        135   S2 AND S3
S5    4342875   (TISSUE(W)TYPE? OR ORGAN? OR CELL?(W)TYPE?)
?s s2 and s5
             541  S2
         4342875  S5
      S6      13  S2 AND S5
```

6/2/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11948262 BIOSIS NO.: 199900194371
Cell type-**dependent and -independent control of HER-2/neu translation.**
AUTHOR: Child Stephanie J; Miller Melanie K; Geballe Adam P(a)
AUTHOR ADDRESS: (a)Divisions of Molecular Medicine and Clinical Research, Fred Hutchinson Cancer Research Center, 1**USA
JOURNAL: International Journal of Biochemistry & Cell Biology 31 (1):p 201-213 Jan., 1999
ISSN: 1357-2725
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

6/2/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07058184 BIOSIS NO.: 000089128288
EXPRESSION **OF THE P185 ENCODED BY** HER2 **ONCOGENE IN NORMAL AND TRANSFORMED HUMAN TISSUES**
AUTHOR: NATALI P G; NICOTRA M R; BIGOTTI A; VENTURO I; SLAMON D J; FENDLY B M; ULLRICH A
AUTHOR ADDRESS: DEP. IMMUNOL., REGINA ELENA CANCER INST., VIALE REGINA ELENA 291, 000161 ROME, ITALY.
JOURNAL: INT J CANCER 45 (3). 1990. 457-461. 1990
FULL JOURNAL NAME: International Journal of Cancer
CODEN: IJCNA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

6/2/12 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

04338038 EMBASE No: 1990226101
Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues
Press M.F.; Cordon-Cardo C.; Slamon D.J.
Department of Pathology, University of Southern, California, 2011 Zonal Avenue,Los Angeles, CA 90033 United States
Oncogene (ONCOGENE) (United Kingdom) 1990, 5/7 (953-962)
CODEN: ONCNE ISSN: 0950-9232
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

```
et     Items   Description
S1         47   MONOCLONAL(W)ANTIBOD? AND FORMULATION AND IN(W)VIVO AND AD-
              MINISTRATION
S2         37   RD (unique items)
S3        334   (LYOPHILIZE? OR FREEZE(W)DRID OR FREEZE(W)DRY) AND MONOCLO-
              NAL(W)ANTIBOD?
S4        161   RD (unique items)
S5   23423699   IN(W)VIVO OR HUMAN?
?s s4 and s5
             161  S4
        23423699  S5
      S6     100  S4 AND S5
```

7/3/10 (Item 10 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

10684812 BIOSIS NO.: 199799305957
The effect of sugars and buffer excipients on the stabilization of a lyophilized **formulation for an anti-IgE** humanized monoclonal antibody.
AUTHOR: Andya James; Wu Sylvia; Hsu Chung; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Research Development, Genentech Inc., South San Francisco, CA 94080**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.):pS78 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996
ISSN: 0724-8741
RECORD TYPE: Citation
LANGUAGE: English

7/3/39 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10114387 Genuine Article#: 484QM No. References: 30
Title: Effect of moisture on the stability of a lyophilized humanized monoclonal antibody **formulation**
Author(s): Breen ED (REPRINT) ; Curley JG; Overcashier DE; Hsu CC; Shire SJ
Corporate Source: Genentech Inc,Pharmaceut Res & Dev,1 DNA Way/S San Francisco//CA/94080 (REPRINT); Genentech Inc,Pharmaceut Res & Dev,S San Francisco//CA/94080
Journal: PHARMACEUTICAL RESEARCH, 2001, V18, N9 (SEP), P1345-1353
ISSN: 0724-8741 Publication date: 20010900
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/40 (Item 2 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09786691 Genuine Article#: 448JN No. References: 40
Title: Modulation of antigenicity related to changes in antibody flexibility upon lyophilization
Author(s): Taschner N; Muller SA; Alumella VR; Goldie KN; Drake AF; Aebi U; Arvinte T (REPRINT)
Corporate Source: Novartis Pharma AG,Biotechnol Dev & Prod,CH-4002 Basel//Switzerland/ (REPRINT); Novartis Pharma AG,Biotechnol Dev & Prod,CH-4002 Basel//Switzerland/; Univ Basel,Biozentrum, Inst Microscopy,CH-4056 Basel//Switzerland/; European Mol Biol Lab,D-69117 Heidelberg//Germany/; Univ London Kings Coll,Dept Pharm,London SE1 8WA//England/
Journal: JOURNAL OF MOLECULAR BIOLOGY, 2001, V310, N1 (JUN 29), P169-179
ISSN: 0022-2836 Publication date: 20010629
Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/41 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09465010 Genuine Article#: 408VL No. References: 34
Title: A specific molar ratio of stabilizer to protein is required for storage stability of a lyophilized monoclonal antibody
Author(s): Cleland JL (REPRINT) ; Lam X; Kendrick B; Yang J; Yang TH; Overcashier D; Brooks D; Hsu C; Carpenter JF
Corporate Source: Genentech Inc,Pharmaceut R&D,1 DNA Way/S San Francisco//CA/94070 (REPRINT); Genentech Inc,Pharmaceut R&D,S San Francisco//CA/94070; Amgen Inc,Dept Pharmaceut,Thousand Oaks//CA/91320; Genentech Inc,Qual Control,S San Francisco//CA/94070; Univ Colorado,Hlth Sci Ctr, Dept Pharmaceut Sci,Denver//CO/
Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 2001, V90, N3 (MAR), P310-321
ISSN: 0022-3549 Publication date: 20010300
Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/89 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10424116 20052396 PMID: 10587113
Freeze-dried formulation for direct 99mTc-labeling ior-egf/r3 MAb: additives, biodistribution, and stability.
Morales AA; Nunez-Gandolff G; Perez NP; Veliz BC; Caballero-Torres I; Duconge J; Fernandez E; Crespo FZ; Veloso A; Iznaga-Escobar N
Center of Molecular Immunology, Havana, Cuba.
Nuclear medicine and biology (ENGLAND) Aug 1999, 26 (6) p717-23, ISSN 0969-8051 Journal Code: BOO
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

7/3/95 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05277337 89306482 PMID: 2744392
Characteristics of lyophilized **anti-A and anti-B** monoclonal antibodies **used for identification of the ABO blood group system]**
Kharakteristika liofilizirovannykh anti-A i anti-B monoklonal'nyk antitel dlia opredeleniia grupp krovi sistemy ABO.
Deriugina EI; Drize NI; Lemeneva LN; Chertkov IL; Gurtovoi IM
Gematologiia i transfuziologiia (USSR) May 1989, 34 (5) p61-4, ISSN 0234-5730 Journal Code: FK6
Languages: RUSSIAN
Document type: Journal Article
Record type: Completed

```
### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 02.08.23D

Last logoff:  28aug02 08:58:32
Logon file001 28aug02 09:44:20
***                                   ***

File   1:ERIC  1966-2002/Aug 08
       (c) format only 2002 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?b 155
       28aug02 09:44:24 User233719 Session D1030.1
            $0.29    0.083 DialUnits File1
     $0.29  Estimated cost File1
     $0.01  TELNET
     $0.30  Estimated cost this search
     $0.30  Estimated total session cost   0.083 DialUnits


File 155:MEDLINE(R)  1966-2002/Aug W4
*File 155: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

      Set  Items  Description
      ---  -----  -----------
?s her2
      S1     916  HER2
?s her(w)2
          44235  HER
        2456012  2
      S2    1293  HER(W)2
?s erbb2
      S3    1148  ERBB2
?s erb(w)b2
           1379  ERB
          16607  B2
      S4     236  ERB(W)B2
?s s1 or s2 or s3 or s4
            916  S1
           1293  S2
           1148  S3
            236  S4
      S5    3362  S1 OR S2 OR S3 OR S4
?s lung(w)(cancer or carcinoma)
         332019  LUNG
         375266  CANCER
         308610  CARCINOMA
```

HER2 expression in lung carcinoma

```
      S6   38734  LUNG(W)(CANCER OR CARCINOMA)
?s s5(s)s6
            3362  S5
           38734  S6
      S7     102  S5(S)S6
?s s7 not py>1995
             102  S7
         3090067  PY>1995
      S8      28  S7 NOT PY>1995
?rd
...completed examining records
      S9      28  RD (unique items)
?ds

Set     Items   Description
S1        916   HER2
S2       1293   HER(W)2
S3       1148   ERBB2
S4        236   ERB(W)B2
S5       3362   S1 OR S2 OR S3 OR S4
S6      38734   LUNG(W)(CANCER OR CARCINOMA)
S7        102   S5(S)S6
S8         28   S7 NOT PY>1995
S9         28   RD (unique items)
?t s9/6/1-28

 9/6/1
10031516   99034861   PMID: 9816029
  Localized adenocarcinoma of the lung: oncogene expression of erbB-2 and
p53 in 150 patients.
Jun 1995


 9/6/2
08833840   96191822   PMID: 8616111
  Molecular genetic tumor markers in the early diagnosis and screening of
non-small-cell lung cancer.
1995


 9/6/3
08624564   95382554   PMID: 7653995
  Up-regulation of urokinase-type plasminogen activator expression by the
HER2/neu proto-oncogene.
Jul-Aug 1995


 9/6/4
08583512   95340299   PMID: 7615356
  Association between RB-1 gene alterations and factors of favourable
prognosis in human breast cancer, without effect on survival.
Apr 21 1995


 9/6/5
08541195   95300268   PMID: 7781111
  [Gene expression of growth factors, growth factor receptor and oncogenes
in human lung cancer cell lines]
Feb 1995


 9/6/6
08513517   95271702   PMID: 7538595
   Enhanced chemoresistance by elevation of p185neu levels in HER - 2
/neu-transfected human lung cancer cells.
May 3 1995
```

9/6/7
08385615 95150499 PMID: 7847823
Establishment and characterization of five human small cell lung cancer cell lines from early tumor xenografts.
Sep-Oct 1994

9/6/8
08364668 95103532 PMID: 7805040
A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression.
Jan 1 1995

9/6/9
08313537 95070178 PMID: 7979412
[Advances in pathobiological research on lung carcinoma]
Nov 1994

9/6/10
08293057 95051086 PMID: 7962174
Colocalization of the p185HER2 oncoprotein and integrin alpha 6 beta 4 in Calu-3 lung carcinoma cells.
Aug 1994

9/6/11
08147112 94282743 PMID: 7912166
HER2 **/neu-derived peptides are shared antigens among human non-small cell** lung cancer **and ovarian cancer.**
Jul 1 1994

9/6/12
08117836 94243246 PMID: 8186664
Oncogene overexpression in non-small-cell lung cancer tissue: prevalence and clinicopathological significance.
Jan 1994

9/6/13
08096855 94219837 PMID: 8166465
The molecular and cellular basis of human lung cancer.
Jan-Feb 1994

9/6/14
08090616 94231684 PMID: 8176843
[Molecular diagnosis of lung carcinoma]
Apr 1994

9/6/15
07879702 94017835 PMID: 8412200
Genetic changes in lung cancer.
1993

9/6/16
07864937 94001483 PMID: 8398710
Expression of topoisomerase II alpha and beta in an adenocarcinoma cell line carrying amplified topoisomerase II alpha and retinoic acid receptor alpha genes.

Oct 1993

9/6/17
07864374 94000870 PMID: 8104437
Inhibition of human lung cancer cell line growth by an anti-p185HER2 antibody.
Oct 1993

9/6/18
07734415 93260725 PMID: 8098377
Correlation of intrinsic chemoresistance of non-small-cell lung cancer **cell lines with** HER - 2 **/neu gene expression but not with ras gene mutations.**
Jun 2 1993

9/6/19
07712015 93242881 PMID: 1300765
[The search for amplification of the ERBB-2 oncogene in human tumors]
Poisk amplifikatsii onkogena ERBB-2 v opukholiakh cheloveka.
1992

9/6/20
07659053 93177677 PMID: 7679945
Immunocytological detection of bone marrow micrometastasis in operable non-small cell lung cancer.
Mar 1 1993

9/6/21
07548209 93074378 PMID: 1444790
Molecular surgery for cancer.
Nov 1992

9/6/22
07497815 93001780 PMID: 1327031
Molecular approaches to prevention and therapy of aerodigestive tract cancers.
1992

9/6/23
07289168 92223017 PMID: 1373318
Amplification of the topoisomerase II alpha gene in a non-small cell lung cancer cell line and characterisation of polymorphisms at the human topoisomerase II alpha and beta loci in normal tissue.
Mar 1992

9/6/24
07273548 92198667 PMID: 1312850
Mechanisms of p185HER2 expression in human non-small cell lung cancer cell lines.
Apr 1992

9/6/25
07055685 91365853 PMID: 1679763
Monoclonal antibody therapy of human cancer: taking the HER2 protooncogene to the clinic.
May 1991

9/6/26
06803503 91105667 PMID: 1670993
Cytogenetic abnormalities and overexpression of receptors for growth factors in normal bronchial epithelium and tumor samples of lung cancer patients.
Jan 1 1991

9/6/27
06638920 90335831 PMID: 1974168
p185neu expression in human lung adenocarcinomas predicts shortened survival.
Aug 15 1990

9/6/28
06360408 90058477 PMID: 2573414
Amplification of protooncogenes in surgical specimens of human lung carcinomas.
Dec 1 1989
?t s9/3,ab/1,2,8,11,12,13

9/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

10031516 99034861 PMID: 9816029
Localized adenocarcinoma of the lung: oncogene expression of erbB-2 and p53 in 150 patients.
Harpole D H; Marks J R; Richards W G; Herndon J E; Sugarbaker D J
Lung Cancer Research Laboratory, Division of Thoracic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jun 1995, 1 (6) p659-64, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA56749; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Historical information and pathological material from 150 consecutive patients with localized adenocarcinoma of the lung was collected to evaluate oncogene expression of erbB-2 and p53, and erbB-2 gene amplification. Pathological material after resection was reviewed to verify histological staging, and patient follow-up was complete in all cases for at least 68 months. Immunohistochemistry of erbB-2 (**HER - 2** /neu) and p53 oncogene expression was performed on two separate paraffin tumor blocks for each patient with normal lung as control. Gene amplification of erbB-2 was measured after DNA extraction from 20-micrometer sections of erbB-2-positive and -negative tumors. All analyses were blinded and included Kaplan-Meier survival estimates with Cox proportional hazards regression modeling. Two adequate blocks of tumor and normal lung were available for 138 (92%) patients. Immunohistochemical identification of expression of p53 was observed in 49 (37%) patients and erbB-2 in 17 (13%) patients. DNA dot blot analyses were performed on 17 erbB-2-positive and 13 randomly selected erbB-2-negative tumors. There was 1 (6%) of 17 erbB-2-positve tumors with 4-fold erbB-2 gene amplification. Actual 5-year survival was 63% and actuarial 10-year survival was 59% for the entire population of 150 patients. Significant univariate predictors ($P < 0.05$) of cancer death were the presence of symptoms, tumor size >3 cm, poor differentiation, visceral pleural invasion, and p53 expression. Multivariate analysis associated symptoms and p53 expression as independent factors with decreased survival. Thus, this project examined p53 and erbB-2 expression in patients with localized adenocarcinoma and associated p53 status with survival. Multicenter collection of data should allow the

development of a model of cancer recurrence in this most common **lung cancer** .

9/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

08833840 96191822 PMID: 8616111
Molecular genetic tumor markers in the early diagnosis and screening of non-small-cell lung cancer.
Jacobson D R; Fishman C L; Mills N E
Department of Medicine, Kaplan Cancer Center, New York University Medical Center, New York, USA.
Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) 1995, 6 Suppl 3 pS3-8, ISSN 0923-7534 Journal Code: 9007735
Contract/Grant No.: K12 CA01713-02; CA; NCI; T32 ES07267-02; ES; NIEHS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Little progress has been made in decreasing **lung cancer** mortality by applying conventional methods to early diagnosis and screening. Recent advances in molecular oncology, however, have provided tools which may be of use in this area. Many genes involved in controlling cell growth and differentiation are abnormal in **lung cancer** cells. Such genes include K-ras, p53, rb, myc, **her2** /neu, and probably one or more tumor suppressor genes on chromosome 3p. The involvement of these genes in **lung cancer** is reviewed. The K-ras oncogene contains a mutation in codon 12 in many cases of non-small-cell **lung cancer** , particularly adenocarcinoma, and is thus a potentially useful **lung cancer** tumor marker. DESIGN; We have developed a highly sensitive, simple assay for ras mutations, and applied it to bronchoalveolar lavage fluid obtained from patients undergoing evaluation for suspected **lung cancer** . RESULTS: In many cases, the ras assay was more sensitive than routine cytology and histopathology, demonstrating that this is a potentially clinically useful assay. CONCLUSION: Molecular genetic tumor markers, including mutations in ras and other genes, and/or immunohistochemical tumor markers, may provide tools which can be applied to bronchoalveolar lavage fluid or sputum, for use in diagnostic tests and in screening programs. The use of such markers may lead to decreased **lung cancer** mortality.

9/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

08364668 95103532 PMID: 7805040
A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression.
Harpole D H; Herndon J E; Wolfe W G; Iglehart J D; Marks J R
Division of Thoracic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.
Cancer research (UNITED STATES) Jan 1 1995, 55 (1) p51-6, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: CA56749; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In order to construct a multivariate model for predicting early recurrence and cancer death for patients with stage I non-small cell **lung cancer** , 271 consecutive patients (mean age, 63 +/- 8 years) who were diagnosed, treated, and followed at one institution were studied. All patients were clinical stage I with head and chest/abdominal computed tomograms and radionuclide bone scans without evidence of metastatic disease. Pathological material after resection was reviewed to verify

histological staging. Follow-up documented the time and location of any recurrence, was a median 56 months in duration, and was complete in all cases. Data recorded included age, sex, smoking history, presenting symptoms, pathological description, and oncoprotein staining for erbB-2 (**HER - 2** /neu), p53, and KI-67 proliferation protein. Immunohistochemistry of oncogene expression was performed on two separate archived paraffin tumor blocks for each patient, with normal lung as control. All analyses were blinded and included Kaplan-Meier survival estimates with Cox proportional hazards regression modeling. Data, including immunohistochemistry, were complete for all 271 patients. Actual 5-year survival was 63% and actuarial 10-year survival was 58%. Significant univariate predictors ($P < 0.05$) of early recurrence and cancer-death were: male sex; the presence of symptoms; chest pain; type of cough; hemoptysis; tumor size > 3 cm diameter (T2); poor differentiation; vascular invasion; erbB-2 expression; p53 expression; and a higher KI-67 proliferation index (> 5%). An additive oncogene expression curve demonstrated a 5-year survival of 72% for 136 patients without p53 or erbB-2, 58% for 108 patients who expressed either oncogene, and 38% for 27 who expressed both ($P < 0.001$).(ABSTRACT TRUNCATED AT 250 WORDS)

9/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

08147112 94282743 PMID: 7912166
HER2 **/neu-derived peptides are shared antigens among human non-small cell** lung cancer **and ovarian cancer.**
Yoshino I; Goedegebuure P S; Peoples G E; Parikh A S; DiMaio J M; Lyerly H K; Gazdar A F; Eberlein T J
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Previously, we have reported a correlation between the expression of HER2/neu and sensitivity to HLA-A2-restricted cytotoxic T-cells (CTL) in ovarian cancer. To investigate the role of HER2/neu in human non-small cell **lung cancer** (NSCLC), we established autologous tumor-specific CTL from tumor-infiltrating lymphocytes of HLA-A2+ **HER2** /neu+ NSCLC patients. These CTL lines specifically recognized HLA-A2+ **HER2** /neu+ autologous and allogeneic NSCLC cell lines as well as HLA-A2+ **HER2** /neu+ heterologous ovarian cancer cell lines. Furthermore, these CTL recognized an overexpressed, **HER2** /neu-derived peptide. From these results, we conclude that HLA-A2 serves as a restriction element in NSCLC. More importantly, at least one **HER2** /neu-derived peptide is a tumor-associated antigen in NSCLC and ovarian cancer.

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Oncogene overexpression in non-small-cell lung cancer tissue: prevalence and clinicopathological significance.
Lorenz J; Friedberg T; Paulus R; Oesch F; Ferlinz R
III. Medizinische Klinik und Poliklinik, Johannes Gutenberg Universitat, Mainz.
Clinical investigator (GERMANY) Jan 1994, 72 (2) p156-63, ISSN 0941-0198 Journal Code: 9207154
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In contrast to small-cell **lung cancer** , few data are available on the role of oncogene overexpression in non-small-cell lung cancers (NSCLC). To determine the prevalence and extent of the transcriptional activation of cancer genes in NSCLC we investigated the level of mRNA of the three important cellular oncogenes-- **erbB2** , Ki-ras, and c-myc--in 39 surgically or endoscopically obtained tumor samples and 24 samples of normal bronchopulmonary tissue taken from the same patients. Tissue RNA was prepared and the specific mRNA analyzed by the highly sensitive nuclease S1 protection assay. Oncogene mRNA in the tumors was quantified by comparison with the homogeneously weak signals in normal lung tissue preparations with densitometry. The presence of two- to four-fold excess RNA was defined as moderate and a greater than fourfold RNA amount as strong gene overexpression. In contrast to normal tissue the oncogene mRNA amount varied considerably among tumors, showing increases up to 64-fold in **erbB2** , 13-fold in Ki-ras, and 57-fold in c-myc. Moderate and strong (in brackets) mRNA overexpression occurred with 33% (33%) in **erbB2** , 36% (18%) in Ki-ras, and 18% (23%) in c-myc. Simultaneous overexpression of two genes was observed with 41% and increased mRNA of all genes tested with 20% of the NSCLC samples. Augmented oncogene mRNA was observed most frequently in large-cell carcinoma. The c-myc overexpression was significantly more prevalent in large-cell cancer than in adenocarcinoma. Tumor differentiation was negatively correlated with c-myc mRNA amounts.(ABSTRACT TRUNCATED AT 250 WORDS)

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The molecular and cellular basis of human lung cancer.

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Lung cancer arises after a series of morphological changes, which take several years to progress from normal epithelium to invasive cancer. The morphological changes progress from hyperplasia, to metaplasia, to dysplasia, to carcinoma in situ, to invasive cancer and finally to metastatic cancer. Multiple molecular changes have been documented in lung cancers, both small cell (SCLC) and non-small cell (NSCLC) types. The number of changes has been estimated to be in double digits. How can so many changes develop in one cell? One possible explanation is the "field cancerization" theory, that states that all or much of the aerodigestive tract epithelium has been mutagenized, perhaps as the result of exposure to tobacco products or other carcinogens. The molecular changes include activation of dominant oncogenes (myc family, K-ras and **HER / 2** /neu genes), as well as loss of recessive growth regulatory genes or anti-oncogenes (p53, and rb as well as unidentified gene or genes on chromosome 3). However, cytogenetic and molecular genetic studies indicate that multiple other specific sites of actual or potential DNA loss may be present in lung cancers. Many of the well characterized molecular changes may function as negative prognostic factors for survival in subsets of lung cancers. Other changes may include development of drug resistance, and production of growth factors and their receptors. It is tempting to associate specific molecular changes with specific morphological changes, as has been attempted in the colon. However, because of the difficulties in serially sampling the respiratory tract, only a modest amount of data has been collected to date. It appears that deletions of chromosome 3p, hyperproliferation and aneuploidy are early changes, while p53 mutations appear later in the preneoplastic cascade. Documentation of intermediate

markers for **lung** **cancer** and prospective studies of their prognostic effects will be necessary for the design of rational chemoprevention trials.
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